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Editorial

Clinical research in hepatocellular carcinoma: Study design and endpoints ☆

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Surgical resection is an accepted treatment for hepatocellular carcinoma (HCC) [1]. However, its applicability is limited by several factors. In the large majority of cases, HCC develops in the context of underlying liver disease, usually in association with cirrhosis. Significant hepatic dysfunction or the presence of clinically relevant portal hypertension has a profound impact on the outcomes after resection. Consequently, the majority of patients with HCC will not be reasonable candidates for resection due to advanced liver disease. In addition, multifocality of the tumor as a result of intrahepatic metastases via microscopic invasion of the portal system often precludes curative resection and is also considered by many centers to be a contraindication to surgical resection. Well selected patients undergoing resection of HCC at an experienced center would be expected to have good outcomes with perioperative mortality below 3%, blood transfusion in less than 10% of cases, and 5-year survival rates of at least 50% [2]. Unfortunately, even in well selected patients, resection is plagued by recurrence rates of approximately 70% at 5 years as a result of occult metastases that were not detected at the time of resection as well as the formation of *de novo* tumors in the remaining cirrhotic liver [2]. Studies have identified numerous predictors of recurrence including vascular invasion, tumor size, presence of satellites, degree of differentiation, as well as alphafetoprotein (AFP) levels. Several strategies to prevent and treat recurrence have been evaluated over the years (Table 1) [3–18]. Although some of them have shown promising initial results, most of these studies have lacked proper study design or an adequate sample size. In addition, even the treatments with positive results have not been adopted in routine clinical practice, not even at the centers that reported the trials. Therefore, clinical trials assessing adjuvant therapies after resection are urgently needed [19].

In this issue of the Journal, we focus our attention on a randomized, multicenter, phase II study by Liu et al. that evaluates the heparanase inhibitor PI-88 as an adjuvant therapy for HCC after curative resection [14]. Patients with a histological diagnosis of HCC undergoing hepatectomy confirmed as curative by a postoperative CT scan were included and randomized to three arms: untreated control group (group A) and two treatment groups: 160 mg PI-88/day (group B) and 250 mg PI-88/day (group C). The primary endpoints were non-recurrence rate and safety and the secondary endpoint was the time to recurrence in the intention-to-treat population. The main result of this study was that after 48 weeks of follow-up, 29 patients (50%) in group A, 35 (63%) in group B and 22 (41%) in group C remained recurrence-free at completion. These differences did not reach statistical significance but met the criteria to proceed with further investigation of PI-88 at the

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Table 1
Studies of neo-adjuvant and adjuvant therapies for resection of HCC.

Study	*n*	Intervention	Outcome
Treatment of micrometastases			
Izumi [3]	50	Postop lipiodol	No difference with control
Wu [4]	52	Preop chemoembolization	No difference with control
Li [5]	94	Postop lipiodol	No difference with control
Yamasaki [6]	97	Preop chemoembolization	No difference with control
Yamamoto [7]	67	Postop 5FU	No difference with control
Khono [8]	88	Postop lipiodol	No difference with control
Ono [9]	108	Postop epirubicin + carmofur	No difference with control
Lai [10]	66	Postop lipiodol	No difference with control
Ueno [11]	21	Postop lipiodol	No difference with control
Takayama [12]	150	Adoptive immunotherapy	Significant decrease in recurrence
Lau [13]	43	Postop I-131 lipiodol	Significant decrease in recurrence
Liu [14]	168	Postop PI-88	No difference with control but evidence for further study
Chemoprevention of de novo HCC			
Muto [15]	89	Polyprenoic acid	Significant decrease in recurrence
Ikeda [16]	20	Interferon	Significant decrease in recurrence
Mazzaferro [17]	150	Interferon	Significant decrease in late recurrence
Lo [18]	80	Interferon	Significant decrease in recurrence

160 mg/day dose. The most frequent adverse events associated with PI-88 were cytopenia, injection site hemorrhage, PT prolongation, and hepatotoxicity-related withdrawals, particularly in patients receiving the higher dose of PI-88. The authors' main conclusions were that PI-88 at 160 mg/day was optimal and safe, and showed preliminary efficacy as an adjuvant therapy for HCC after resection. A more comprehensive trial of PI-88 at 160 mg/day in this clinical setting was suggested.

The design of clinical trials in HCC is a complex issue: inclusion criteria are frequently heterogeneous, diagnostic criteria are not always standardized, and stratification by well-known prognostic factors is usually omitted. These concerns have made it difficult to compare, analyze and interpret results of reported studies. Furthermore, the selection of appropriate primary and secondary endpoints is crucial for capturing benefits in outcomes that might be achieved with these new interventions. As a consequence, only a few medical interventions have been rigorously tested in the treatment of HCC. In fact, a study reviewing randomized trials in HCC found that two-thirds of these studies had less than optimal study designs and methodology [20].

The current study published by Liu and coworkers adds yet a new piece to the puzzle of HCC treatment and opens the door for evaluating the heparanase inhibitor PI-88 in a larger, phase III trial. The authors should be congratulated for their selection of a randomized phase II trial projected according to the Simon's 2-stage optimal design [21] for testing a new drug since this type of study minimizes the likelihood of erroneous conclusions regarding efficacy. The execution of a single arm, non-randomized phase 2 study would probably have lead to a negative study and, perhaps, would have curtailed the evaluation of a promising drug.

Some may argue that ideally, only compounds found to have effect in trials on patients with advanced HCC should be used in an adjuvant setting. However, one must keep in mind the mechanism of action of the drug being studied. PI-88 is proposed to block the ability of the cancer to degrade heparan sulfate in the extracellular matrix and thus prevent the tumor from developing metastases. Thus, it may be possible for PI-88 or other drugs to be an effective adjuvant therapy without having significant impact on advanced cases of HCC.

However, the readers should keep in mind several issues when examining this study. First, the inclusion criteria called for all patients with a histological diagnosis of HCC undergoing curative hepatectomy as confirmed by a postoperative CT scan. There were no inclusion or exclusion criteria based on tumor stage. As a result, a patient's suitability for resection was determined by each individual center. As long as the patients had a postoperative CT scan demonstrating no residual HCC, they could be enrolled into the study. Consequently, the study population was quite heterogeneous with a large proportion of the patients having advanced HCC (micro or macrovascular invasion in 39/168 cases, multinodular or massive HCC in 38/168 patients). It is critical to select a homogeneous patient population for the evaluation of new agents. Otherwise, the results of clinical trials will be difficult to interpret since differences in outcome due to the intervention can be lost due to vast differences in the expected natural outcomes of patients. Random effect from the inclusion of such a heterogeneous patient population may explain why PI-88 at the higher dose was not found to be effective. Trials assessing the efficacy of new drugs being used as adjuvant therapy after radical treatment should ideally include patients with early HCC. Well-defined and

pre-established inclusion criteria should be clearly provided, avoiding decisions by individual centers that can only lead to selection biases. The Barcelona Clinic Liver Cancer (BCLC) prognosis system [22] has emerged during recent years as the standard classification that is used for trial design and clinical management of patients with HCC [1,19], and in this setting, the inclusion of BCLC stage 0-A patients will help to select a homogeneous patient population. Furthermore, in studies that have tissue specimens available, patients should be stratified for high or low risk of recurrence prior to randomization. Patient stratification should ideally be performed based on well-established predictors of recurrence such as the presence of vascular invasion, satellite nodules, tumor multinodularity, and poor differentiation.

Another key point in the design of phase II trials in HCC is the selection of appropriate primary and secondary endpoints. Proper selection of these endpoints is critical for capturing potential benefits of the new interventions. This statement is particularly true with the advent of targeted agents, which usually have a cytostatic effect by arresting tumor growth. These types of agents may have benefit in terms of survival with no measurable response rate. Thus, for these type of therapies, a time-to-event endpoint may be better able to detect a benefit. In the current study, the authors have chosen non-recurrence at 48-week of follow-up as the primary endpoint which may be insufficient to detect a potential benefit. Some drugs may act vigorously in delaying but not avoiding the appearance of recurrences, thus translating into a significant improvement in survival without actually reducing the recurrence rate. Under the current study design, the benefit of such agents may be disregarded and their evaluation could be prematurely terminated because of an apparent lack of efficacy. We are convinced that the best primary endpoint in this study would have been time to recurrence.

Nevertheless, we should not lose sight of the accomplishment of the authors. Randomized and controlled trials in the field of HCC are difficult to conduct and thus sorely lacking and desperately needed. The authors should be commended for having conducted a study that fulfills the criteria put forward by the CONSORT statement [23]. In addition they have chosen to evaluate their agent with a randomized phase II trial before proceeding with a large and expensive phase III trial. Unfortunately, their selection of a suboptimal endpoint and inclusion of a heterogenous population makes it difficult to come to robust conclusions. Based on the authors findings, PI-88 was moved forward to a Phase III trial which has, unfortunately, closed early and prior to completion.

The success of sorafenib in the treatment of advanced HCC has opened the door for the use of such small targeted molecules in the adjuvant setting [24]. As more and more of such small molecular therapies are developed, there will be a growing need for studies to evaluate their efficacy in the treatment of HCC. It will be more important than ever to conduct well-designed trials with properly selected patients and endpoints, not only to capture their potential benefits but also to prevent waste of limited resources.

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